PRODUCT: XADAGO (Safinamide)
STATISTICAL ANALYSIS PLAN PROTOCOL NUMBER: USWM-SA1-4001

SPONSOR:

MDD US Operations, LLC, a subsidiary of Supernus Pharmaceuticals, Inc.
9715 Key West Avenue
Rockville, Maryland 20850

TITLE:

A Prospective, Observational Study to Evaluate Changes in Non-Motor Symptoms and other Clinical Outcome Assessments of Parkinson's Disease Patients Treated with XADAGO (safinamide) Tablets

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STUDY DRUG:

XADAGO (SAFINAMIDE)

PROTOCOL NUMBER:

USWM-SA1-4001

STUDY TITLE:

A Prospective, Observational Study to Evaluate Changes in Non-Motor Symptoms and other Clinical Outcome Assessments of Parkinson's Disease Patients Treated with XADAGO (safinamide) Tablets

SPONSOR:

US WorldMeds, LLC

4441 Springdale Road
Louisville, KY 40241

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CMH	Cochran Mantel-Haenszel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DOB	Date of Birth
dy	Days
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transferase
ICD-9	International Classification of Diseases – 9th Edition
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities Terminology
mo	Months
N	Total Sample Size
NIMH	National Institute of Mental Health
OC	Observed Cases
OTC	Over the Counter Medication
PCS	Potential Clinical Significance
PP	Per-Protocol Population
S	Sex
s.d.	Standard Deviation

Table 1: List of Abbreviations (Continued)

Abbreviation	Term
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SR	Sustained Release
TG	Treatment Group
TS	Transdermal Delivery System-Placebo
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell Count
WHO	World Health Organization
yr	Years

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol USWM-SA1-4001.

Protocol Revision Chronology:		
Protocol	28-AUG-2017	Original
Protocol	01-NOV-2017	Amendment 1
Protocol	12-OCT-2018	Amendment 2

This SAP was developed in accordance with ICH E9 guidelines. All decisions regarding final analysis, as defined in this SAP document, will be made prior to Database Freeze (unblinding) of the study data. Further information can be found in the protocol.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

The objective of this prospective, observational study is to gather real-world observational data from the following assessments in individuals in the United States (US) with Parkinson's disease (PD) during XADAGO treatment: the Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS), the Parkinson's Disease Questionnaire (PDQ-39), the Montreal Cognitive Assessment (MoCA), the Treatment Satisfaction Questionnaire for Medication (TSQM-9), the Clinical Global Impression of Change (CGI-C), and the Patient Global Impression of Change (PGI-C).

3.2. Study Endpoints

Study endpoints are the changes from the Baseline Visit to Visit 3 (Study Day 60, Primary Endpoint) in motor and non-motor symptoms, general health status/quality of life, treatment satisfaction, and global impression as measured by MDS-UPDRS, PDQ-39 and MoCA, TSQM-9, CGI-C and PGI-C, respectively.

4. STUDY DESIGN

4.1. Summary of Study Design

This is a multisite, prospective, observational study to evaluate clinician-reported outcomes (ClinROs) and patient-reported outcomes (PROs) related to motor and non-motor symptoms, health status/QoL, and treatment satisfaction in a "real world" PD population in the US newly prescribed XADAGO in accordance with the Package Insert indication. The decision to prescribe XADAGO by clinician and patient must be made before site study staff discuss the study with the patient. If the patient is interested in participating in the study, an informed consent form (ICF) will be provided to the patient for review, contents of the ICF will be discussed, and patient's signature will be obtained. Enrolled patients will be prospectively followed for 2 months, with the potential to participate in a 4-month Extension Study.

The Schedule of Assessments (Table 2) presents all the study activities that will occur at each study interaction with patients during clinic visits, by telephone at protocol-specified time points, and by PRO via the electronic Clinical Outcome Assessment (eCOA) system. Investigative sites will be provided secure access to 21 CFR Part 11-compliant electronic Case Report Forms (eCRF), and sites and patients will have access to the eCOA system(s) for collecting all patient data.

4.2. Definition of Study Drugs

The study drug that will be used in the trial is Safinamide.

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

Since this is an observational study, sample size is determined based on clinical judgment. Up to 600 patients are planned for screening. This is expected to result in a final sample size of up to 540 eligible and evaluable enrolled patients, distributed among approximately 30 investigative sites in the US.

4.3.2. Sample Size Re-estimation

Not applicable.

4.4. Randomization

This is not a randomized study.

4.5. Clinical Assessments

Table 2: Schedule of Assessments

Protocol Activity *(Visit Type, Location, and Number; Study Day and Month; Window Allowance)*	2-Month Main Study			4-Month Extension Study		
	Screening/Baseline Assessment Visit [a]	Follow-up	Primary Endpoint Visit	Follow-up	PRO Assessment Only	Follow-up
	Clinic	Telephone	Clinic	Clinic		Clinic
	Visit 1	*Visit 2*	*Visit 3*	*Visit 4*	*Visit 5*	*Visit 6*
	Day 1	*Day 30*	*Day 60*	*Day 90*	*Day 120*	*Day 180*
	Month 1		*Month 2*	*Month 3*	*Month 4*	*Month 6*
	±7 days	*±2 days*	*±7 days*	*±7 days*	*±7 days*	*±14days*
Informed Consent and HIPAA Authorization	X					
Eligibility: Inclusion/Exclusion Criteria	X					
Medical History and Demographics	X					
Medical History of PD, other Neurological Conditions	X					
Presentation of Study Instructions to Patient	X					
Registration and Training on eCOA System	X					
Concomitant Medications Assessment[b]	X	X	X	X		X
XADAGO Administration Compliance Review[b]		X	X	X		X
PRO Compliance Review[b]			X	X		X
Adverse Events Assessment[b]			X	X		X
MDS-UPDRS[b]	X		X	X		X
PDQ-39[c]	X		X	X		X
MoCA[b]	X		X			X
TSQM-9[c]		X	X	X	X	X
CGI-C[b]			X	X		X
PGI-C[c]			X	X		X

[a] Screening will take place not more than 7 days before the Baseline Visit and may occur at the same time as the Baseline Visit. The first study dose of XADAGO will occur in the clinic on the Baseline Visit day, which will be designated Study Day 1.

[b] Assessments to be administered by the PI/certified or HCP designee.

[c] Assessments to be completed by the patient, with Care Partner assistance, if required.

5. PLANNED ANALYSES

5.1. Interim Analyses

Interim data analyses will be performed periodically to provide study updates and to support potential presentation of interim results
. Since this study is observational only and treatments are not assigned to specific patient/treatment groups, these interim analyses will have no statistical implications.

5.2. Final Analyses

After the last enrolled subject completes Visit 3, the database will be locked. The final analyses will be performed after the database lock.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings (e.g., post text tables and individual subject data listings are prepared according to ICH Guideline E3) include a "footer" providing explanatory notes which indicate at a minimum:

1. Date of data extraction.
2. Date of output generation.
3. SAS program name, including the path that generates the output.
4. Any other output specific details that require further elaboration.

Post text tables also include reference(s) to the subject data listing(s) that supports the summary data. The data extraction date links the output to the archived database that is locked to ensure replication of the results.

In general, row entries in post text tables are made only if data exists for at least one subject (e.g., a row with all zeros will not appear). The only exception to this rule applies to tables that summarize the study termination status of subjects (e.g., reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied. The summary tables clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

Summary tables for medications and medical conditions are coded according to standard dictionaries (e.g., WHO Drug standard dictionary). Adverse event preferred terms and body/organ systems are coded using the latest MedDRA dictionary. The MedDRA dictionary can be used, as well, in the coding of signs and symptoms, medical history, physical examination abnormalities, and clinical diagnoses.

Supportive individual Subject Data Listings, at a minimum, are sorted and presented by investigational site (center). Listings also include subject number, visit number, and visit date.

Other subject data listings that do not support a specific summary table are included to provide an enumeration of the investigator's general comments. This listing is also organized by investigator. Sorting is also performed with respect to subject, reference visit number and date, visit relative day, date of the comment, and the text of the comment.

Imputed or derived data will be flagged in the individual subject data listings. Imputed data are not incorporated into any raw or primary datasets. These data are retained in derived analysis datasets.

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

The default convention is to number tables and listings using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with two digits per level (e.g., Table XX.YY.ZZ. …).

1. The first level number should be consistent with the corresponding CSR appendix in which the tables or listings will appear. For example, the post text tables usually occupy Appendix 14 and the individual subject data listings are put in Appendix 16. All post text tables should have a main number level 14 and listings 16. The subject accounting and disposition table is usually first in the first section of the report and should be numbered Table 14.1. The supportive subject data listing would be Listing 16.1. A subset by sex table would have the number Table 14.1.2, etc.
2. Subject accounting and final disposition should appear as the second level number (Table 14.1 series). Baseline and demographic profile occupy the next sub-level (Table 14.2 series). Efficacy should come next (14.3 series) followed by safety (table 14.4 series). Reasons for subjects' being excluded from efficacy and protocol violation summary tables should appear as the last level (Table 14.5 series). Similar conventions should be applied to the subject data listings.
3. The title should be complete, accurate, and concise. The last line of the title should provide the analysis group being summarized (e.g., Intent-to-Treat Subjects or Per-Protocol Efficacy Subjects). If possible, the units of measurement for data contained in the table can appear in parentheses to conserve space in the body of the table.

   Whether in the title or body of a table or listing, units must always be specified for all appropriate data.
4. If possible, variables being summarized and statistics reported should appear in the left most column of a table. In general, the listings should be sorted and presented by investigational site, and subject number. Site can appear in the banner of the listing. From left to right, the subject number, visit number, visit date, and relative day should appear. All tables and listings must have explanatory notes that give, at a minimum, data extraction date, output generation date, complete program name and path where it is stored, CRF pages from which the data were obtained, and supportive listings or tables supported, as appropriate. The definition of all derived variables and decodes for coded data must appear in the notes. Due to space limitations, tables and listings may require a page of notes as a one-time preface to the output.

6.3. Data Management

IBM Clinical Development is the software platform used for Electronic Data Capture (EDC). Derived datasets are created using (SAS®) software. Data analyses and summary tables are generated using SAS version 9.4 or above.

6.4. Data Presentation Conventions

Continuous variables (e.g. age) are summarized using descriptive statistics (the number of subjects with available data, the mean, standard deviation (SD), median and minimum and maximum). Categorical variables (e.g. race) are summarized using counts and percentages. Percentages are calculated using the total subjects in the XADAGO group.

The following conventions are applied to all data presentations and summaries.

- For continuous variables, all mean and median values are formatted to one more decimal place than the measured value. Standard deviation values are formatted to two more decimal places than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value.
- For categorical variables, the number and percentage of responses are presented in the form XX (XX.X%) where the percentage is in the parentheses.
- Date variables are formatted as DDMMMYYYY for presentation. Time is formatted in military time as HH:MM for presentation.
- Wherever possible, data will be decimal aligned.
- Unless otherwise stated, any statistical tests performed will use 2-sided tests at the 5% significance level.

The table and listing shells and table of contents as part of this SAP provide the expected layout and titles of the tables, listings and figures. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation. The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

6.5. Analysis Populations

6.5.1. Screen Failures

All subjects will be enrolled into the study. There are no screen failures.

6.5.2. Safety Population

The ‘Safety Population’ is defined as all subjects who sign informed consent for the study, complete baseline assessments, and receive at least 1 dose of XADAGO.

6.5.3. ITT Population

The ITT Population is defined as all subjects who sign informed consent for the study, complete baseline assessments, and receive at least 1 dose of XADAGO. ITT population will be used to analyze all efficacy endpoints except MDS-UPDRS.

6.5.4. Evaluable Population

The Evaluable population comprises all subjects in the safety population who complete at least the MDS-UPDRS assessment at the Study Day 60 visit. Evaluable population will be used to analyze MDS-UPDRS endpoint.

6.6. Baseline Assessments

Baseline assessments are defined as the last non-missing result prior to administration of the first dose of study medication. For continuous variable, if multiple measurements were done at the same date without time variable collected, baseline will be defined as the average of multiple measurements on the same date. For lab parameters, all lab results, including local and central lab ones, will be used to derive the baseline value.

6.7. Derived and Transformed Data

6.7.1. Baseline Age

Subject's age in years will be calculated based on date of informed consent date using the following formula:

Age (year) = FLOOR((date of informed consent – date of birth)/365.25*12))

where FLOOR( ) function returns the integer part of the result.

6.7.2. Study Day

If the date of interest occurs on or after the first dose date, study day will be calculated as (date of interest – date of first dose) + 1. If the date of interest occurs prior to the first dose date, study day will be calculated as (date of interest – date of first dose). There is no study day 0.

6.7.3. Change from Baseline

Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as (change from baseline/baseline result * 100).

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

6.7.4. Visit Windows

Visit windows were +- 7 Days for Baseline, Visit 3, Visit 4 and Visit 5; +- 2 Days for Visit 2 and +-14 Days for Visit 6.

6.7.5. Multiple Assessments

When multiple assessments are collected on the same date, the average of those assessments will be used in the analyses.

6.8. Handling of Missing Data

6.8.1. Missing Efficacy Endpoints

The missing efficacy data will be imputed by Last-Observation-Carried-Forward (LOCF) method.

7. STUDY POPULATION

7.1. Subjects Disposition

The disposition of all subjects will be summarized by cohort and site. Subject disposition tables will include the number and percent of subjects who were:

- included in each analysis populations (Safety, Evaluable);
- discontinued from the study early, summarized by primary reason for discontinuation.

The number of subjects screened and number of days in the study of each subject will also be summarized by cohort and overall.

Frequency and percentages of patients completing and discontinuing the study prior to the primary endpoint (Study Day 60) and prior to the last study visit (Study Day 180) will be analyzed by cohort and overall.

7.2. Protocol Deviations

At the discretion of the sponsor, major protocol violations as determined by a review of the data of the study results and the conduct of statistical analyses may result in the removal of a subject's data from the PP Populations. The sponsor, or designee, will be responsible for producing the final protocol violation file this file will include a description of the protocol violation, and clearly identify whether or not this violation warrants exclusion from the Evaluable Population.

All protocol deviations by type of deviations will be summarized by cohort and overall.

7.3. Demographic and Baseline Characteristics

All subjects in the safety population are included in the post text table which summarizes the subject population, and for all treated subjects by cohort and overall, with respect to age at entry into the study, age at onset of the condition under study, sex, race, weight, height, body temperature, any primary diagnostic criteria and/or secondary co-morbid diagnoses.

Age will be reported in years and summarized with descriptive statistics N, mean, s.d., median, and range (e.g., minimum and maximum values), and as a frequency distribution in the groups of 30-<65 and >65 years.

7.4. Medical History Present at Entry

Medical history information will be coded using the latest MedDRA dictionary and summarized by treatment (50 mg vs 100 mg), by cohort and overall for the safety population using descriptive statistics. No formal statistical comparisons will be performed.

7.5. Prior Medication History and Medications Present at Entry

Prior medication is defined as the medications stopped before the first dose date. Prior medications taken during the study will be coded using the latest WHO Drug dictionary and will be summarized by ATC level 2, ATC level 4 and preferred term for each cohort and overall.

A by-subject listing of prior medication data will be presented.

8. EFFICACY

8.1. Testing Statistical Assumptions Including Comparability at Baseline

For baseline data, univariate statistics will be generated for continuous data (e.g., age, height, weight, body temperature, the efficacy assessment scales, subscales, and factors) in order to examine the nature of the underlying statistical distributions and identify the extent to which outliers affect the distributions.

8.2. Subgroup Analyses

No subgroup analyses will be done in this study.

8.3. Multiple Comparisons and Multiplicity

No multiplicity issue in this study.

8.4. Analysis of the Efficacy Endpoint

The change in MDS-UPDRS, PDQ-39, and MoCA from the Baseline Assessment Visit to the Primary Endpoint (Study Day 60) will be summarized by cohort and overall. An analysis of paired t-test will be used to analyze the continuous endpoints.

9. SAFETY AND TOLERABILITY

The analysis of safety and tolerability data includes an overall summary of tolerability, adverse event preferred terms by body/organ system, drug exposure (duration of treatment) by treatment (50 mg vs 100 mg), dosing information/compliance, concomitant medications, clinical laboratory results, vital signs, physical examination, and study termination status. Tables summarizing the adverse events reported by subjects who died, experienced non-fatal serious adverse events (SAE), or prematurely discontinued the study due to adverse event (AEs) will be prepared. Summaries of potentially clinically notable laboratory results and vital sign abnormalities will be presented. Paired subject data listings will be provided to support the summaries of SAEs s and these will be sorted first by subject and then by event preferred term or parameter.

9.1. Overall Summary of Tolerability

The overall summary of tolerability table presents the data for all treated subjects by cohort and overall. Entries in this table are the number of:

1. Subjects treated and subject months of drug exposure by treatment (50 mg vs 100 mg).
2. Subjects with adverse events.
3. Adverse events.
4. Subjects with serious adverse events.
5. Subjects discontinuing due to adverse events.
6. Deaths.

The subject data listing provides a complete disclosure of adverse events as recorded in the CRF and supports this table and all other AE summary table subsets.

9.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

AEs will be presented according to a treatment emergent signs and symptoms algorithm. These events are first observed after the initiation of study drug and are captured until the follow-up visit. Adverse events will be counted if they occur no more than 2 days after the cessation of treatment for non-serious events and within 30 days following the cessation of treatment for serious events.

9.2.1. Summaries of Adverse Event Incidence Rates for All Subjects

The primary presentation of AEs data is prepared without regard to causality or relationship to study medication and classifies events using the most recently available MedDRA dictionary with respect to preferred term and body/organ system for all treated subjects by cohort and overall. Subjects will be counted only once at the body system level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a subject will be counted only once. Subjects who experience more than one event within the same body system are counted once at each preferred term level.

Supplementary tables summarize the events with respect to the maximum severity observed for each preferred term and highest relationship to study medication by cohort and overall. The presentation of adverse events with respect to the severity or intensity of the event usually categorizes the data as mild, moderate, or severe.

The relationship of the event to study medication will be collapsed into two categories, related and not related:

1. Related combines the options possible, probable, and highly probable.
2. Not related is a combination of unlikely and not related.

A by-subject listing of serious adverse event data will be presented.

9.2.2. Missing and Partial AE Onset Dates

The start dates for AEs are important for the:

1. Treatment emergent algorithm.
2. Designation of unique AE occurrences.

Completely missing or partially missing AE onset dates will be imputed. The imputation rule is described in Section 6.8.1.

Imputed dates will be flagged in the individual supportive subject listings.

9.2.3. Summaries of Adverse Incidence Rates for Serious Adverse Events (SAE), Adverse Event Dropouts, and Death

Adverse event incidence rates, by body system , will be summarized for subjects who report a non-fatal serious adverse event, discontinue treatment prematurely due to an adverse event, and deaths.

A by-subject listing of premature discontinuations due to all causality will be presented.

9.3. Study Termination Status

This post text table categorizes the status of the subjects at the end of the study. The completion status is summarized with respect to the number of subjects by cohort and overall:

1. Completing the entire course of treatment.
2. Discontinuing the trial prematurely.
3. Reason for premature study termination.

The reasons for early study termination are adverse event, protocol violation, screen failure, administrative, lack of efficacy, lost to follow-up, death, other, etc.